REMARKS

Reconsideration and withdrawal of the rejections of the claims, in view of the amendments and remarks herein, is respectfully requested. Claims 1-2 and 20 are amended, and claim 47 is canceled. The amendments are intended to advance the application and are not intended to concede to the correctness of the Examiner's position or to prejudice the prosecution of the claims present prior to amendment, which claims are in a continuing application of the above-identified pending application. Claims 1-23 and 25-46 are now pending.

The 35 U.S.C. § 112 Rejections

Claim 47 was rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement (a "new matter" rejection). This rejection, as it may be maintained with respect to the pending claims, is respectfully traversed.

Although claim 47 is canceled, the subject matter of claim 47 is incorporated into claim 1.

The Examiner is requested to consider Figure 11 in the application and in particular vectors identified with "CL1" and "PEST". Those vectors have two different protein destabilization sequences located C-terminal to the reporter protein.

Therefore, withdrawal of the § 112(1) "new matter" rejection is respectfully requested.

Claims 1-11, 15-16, 18-20, 25, 30-32, 34-37, 41-44, and 47 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner asserts that the specification only describes a polynucleotide having the nucleic acid sequence of SEQ ID NO:72, which encodes a fusion polypeptide comprising a specific luciferase isolated from firefly, a specific PEST sequence, and a specific CL1, and so does not constitute a representative number of species to describe polynucleotides encoding a fusion polypeptide comprising a whole genus of variants, recombinant and mutants of any or all reporter protein or luciferase and any or all protein and/or mRNA destabilization sequences. This rejection is respectfully traversed.

The documents submitted with the Amendment filed on March 29, 2007, as well as the references cited against the claims under 35 U.S.C. § 103(a), clearly evidence that sequences for

reporter proteins, protein destabilization sequences and mRNA destabilization sequences were known to the art. Applicant need not describe what is known to the art. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 231 U.S.P.Q. 81, 94-95 (Fed. Cir. 1986).

Moreover, the Examiner has failed to explain why those documents and references are not sufficient to show that sequences for reporter proteins, protein destabilization sequences and mRNA destabilization sequences were known to the art. See M.P.E.P. § 2163.04(II).

What is required to provide an adequate written description for a claimed genus, is that the specification provides a sufficient description of a representative number of species by an actual reduction to practice, reduction to drawings or by a disclosure of relevant, identifying characteristics, i.e., by a structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics (Guidelines for Examination of Patent Applications under the 35 U.S.C. § 112(1) Written Description Requirement, Fed. Reg., 66, 1099 (2001)). Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that Applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. (Fed. Reg., December 21, 1999 (Volume 64, Number 244).

The properties (attributes) that identify the genus of nucleic acid molecules are that the sequences in the nucleic acid molecules are those for a reporter protein, and a protein destabilization sequence and/or RNA destabilization sequence, or combinations thereof. Underlying each of these properties is a structure. That is, not every nucleotide sequence encodes a reporter protein; not every nucleotide sequence present in a larger nucleotide sequence, once translated to a protein, confers a decreased half-life upon the translated protein; and not every nucleotide sequence present in a larger nucleotide sequence, once transcribed, confers a decreased stability to the resulting mRNA.

Further, the specification exemplifies three different firefly luciferase sequences (structure) (SEQ ID NOs: 48, 49, and 66), two different click beetle luciferase sequences (structure) (SEQ ID NOs: 77 and 79), a *Renilla* luciferase sequence (structure) (SEQ ID NO:47), a green fluorescent protein sequence (structure) (SEQ ID NO:68), as well as other reporters (see page 4 of the specification), numerous protein destabilization sequences (structure) and sources

of other protein destabilization sequences (see pages 5 and 23 in the specification), and numerous RNA destabilization sequences and sources for other such sequence (see page 6 of the specification). One of skill in the art in view of Applicant's disclosure can recognize other members of "reporter protein", "protein destabilization sequence" and "RNA destabilization sequence" in view of the species disclosed in Applicant's specification.

The Examiner is respectfully requested to reconsider that specification at issue in Univ. Calif. v. Eli Lilly and Co., 119 F.3d 1559, 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997) *did not disclose a nucleotide sequence for the claimed human cDNA and disclosed only one rat cDNA sequence for the claimed vertebrate or mammalian cDNAs*. In contrast to the claims at issue in Eli Lilly, Applicant discloses numerous nucleotide sequences falling within the scope of the claimed genus, as discussed above.

Moreover, in the Amendment mailed on November 15, 2007, the Examiner was requested to consider that the terms at issue in the present application are not new or unknown biological material that the skilled artisan could easily miscomprehend. In Amgen v. Hoechst Marion Roussel, 314 F.3d 1313, 65 U.S.P.Q.2d at 1398 (Fed. Cir. 2003), the Federal Circuit pointed out that in Enzo Biochem. v. Gen-Probe, Inc., 296 F.3d at 1324, 63 U.S.P.Q.2d at 1613 (Fed. Cir. 2002), it was clarified that Eli Lilly did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure. The Federal Circuit continued stating that both Eli Lilly and Enzo Biochem. are inapposite to Amgen because the claim terms at issue ("vertebrate" and "mammalian") were not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend because they readily "convey distinguishing information concerning [their] identity" such that one of ordinary skill in the art could "visualize or recognize the identity of the members of the genus." Eli Lilly, 119 F.3d at 1567, 1568, 43 U.S.P.Q.2d at 1406. The words "reporter protein", "protein destabilization sequence" and "mRNA destabilization sequence" readily convey distinguishing information concerning their identity such that one of ordinary skill in the art can visualize or recognize the identity of the members of the genus.

In the Office Action dated January 23, 2008, the Examiner did not provide reasoning why, in view of Amgen, the phrase "reporter protein", "protein destabilization sequence" and "mRNA destabilization sequence", which clearly convey distinguishing information concerning identity as discussed above, do not satisfy the written description requirement of § 112(1).

Accordingly, withdrawal of the § 112(1) "written description" rejection is respectfully requested.

The 35 U.S.C. § 103 Rejection

Claims 1-11, 15-20, 25, 30-32, 34-37, 41-44 and 47 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Leclerc et al. (BioTechniques, 29:590 (2000)), Corish et al., Protein Eng., 12:1035 (1999)), Gilon et al. (EMBO J., 17:2759 (1998)) and Kastelic et al. (WO 00/39314). As this rejection may be maintained with respect to the pending claims, it is respectfully traversed.

Leclerc et al. prepared a construct in which a coding sequence for a firefly luciferase was linked to a C-terminal murine ornithine decarboxylase (mODC) coding sequence that includes a PEST sequence found near the C-terminus of wild-type mODC. It is disclosed that the PEST sequence in mODC corresponds to residues 423-450, and that residues 423-461 of mODC (modified by an amino acid substitution at two positions), i.e., the C-terminal residues of mODC, were fused to firefly luciferase sequences (see Figure 1).

Leclerc et al. reports that the half-life of the firefly luciferase with the PEST sequence was 0.84 hours. It is disclosed that the construct allows for detection of rapid increases or decreases in gene expression (abstract), such as those which are transient dynamic changes or in response to gene inhibiting or activating secretagogues (page 600). The authors note that other factors such as mRNA stability and processing influence reporter activity.

Corish et al. disclose constructs encoding green fluorescent protein (GFP) linked at the C-terminus to a 27 amino acid sequence from murine ODC that contains a PEST sequence or linked at the N-terminus to a 116 residue fragment from cyclin B1 that contains a destruction box (CDB), or both. Notably, the presence of both CDB and ODC sequences (at the N-terminus and at the C-terminus, respectively) resulted in a GFP protein having a half-life that was substantially the same (i.e., no additive or complementing effect) as the GFP protein with only the CDB

sequence (see Figure 2). Thus, it appears that the presence of the CDB sequence, which leads to ubiquitination at the N-terminus of GFP, dictates the half-life of the CDB-GFP-ODC fusion protein.

Gilon et al. report on the isolation of a set of protein degradation signals for ubiquitin based proteolysis in yeast.

Kastelic et al. disclose a construct having a coding region for luciferase linked to a mRNA instability sequence (clone # 63) and its use in a method to screen for compounds that promote the instability of mRNAs with mRNA instability sequences. The effect of the mRNA instability sequence on luciferase expression in the results shown in Figure 4 is not particularly apparent until 24 hours after differentiation is induced, although the overall signal of clone # 63 is 3- to 5-fold less than the control clone (clone # 53, which has a luciferase construct but no mRNA instability sequence). With reference to this data, it is disclosed that one "would expect in the case of luciferase to see a weaker effect of mRNA destabilizing drugs since transcription remains high" (page 12).

Treatment of the clones with an agent known to promote the instability of mRNAs (a radicicol analog, i.e., SDZ 216-732) resulted in a decrease in activity in clone #63 over time (Figure 5 in Kastelic et al.). Treatment of the clones with actinomycin D (an agent that binds DNA at the transcription initiation complex and prevents elongation) resulted in a decrease in activity for both clones but relatively less of a reduction for clone # 63, while treatment of the clones with cycloheximide (an agent that inhibits protein synthesis) resulted in a decrease in activity clone # 53 and an increase in activity for clone # 63 (Figure 5).

If there are fewer luciferase mRNAs available for translation in clone # 63 cells as a result of the mRNA instability sequence, it is unclear why clone # 63 has more activity than clone # 53 in the presence of actinomycin D or cycloheximide at 8 hours. Moreover, the reduced activity for clone # 63 in the presence of SDZ 216-732 relative to clone # 53 at 8 hours in Figure 5 may be due to the reduced signal for clone # 63 (see Figure 4).

One of skill in the art would not look to combining different types of destabilization sequences in view of the combination of Leclerc et al., Corish et al., Gilon et al. and Kastelic et al. With regard to combining different protein destabilization sequences, given that the half-life of the fusion protein in Corish et al. is almost exclusively the result of the presence of the CDB

sequence, there would be no motivation to combine protein destabilization sequences as there was little benefit in Corish et al. to the presence of a different protein destabilization sequence in decreasing protein half-life, even though the two protein destabilization sequences may be mechanistically different.

Prior to Applicant's disclosure it was unknown whether different protein destabilization sequences could have complementing effects. And in view of Corish et al., it was unexpected that different protein destabilization sequences could have complementing effects. Moreover, prior to Applicant's disclosure, it was unknown if two different protein destabilization sequences at the C-terminus of a reporter protein would result in a reporter protein with a half-life that was different than a reporter protein with one of the protein destabilization sequences.

With regard to combining protein and mRNA destabilization sequences, the purpose of the two types of destabilization sequences is different. As transcription preceeds RNA processing and RNA processing preceeds translation, a mRNA instability sequence decreases the amount of translatable mRNA, which in turn decreases the amount of translated protein, but the half-life of the translated protein is unaltered. For constructs with a mRNA destabilization sequence, this allows for screening of agents that promote mRNA destabilization (see Kastelic et al.). The presence of a protein destabilization sequence in a translated protein targets the protein for more rapid degradation than a corresponding protein without the protein destabilization sequence. A construct with a protein destabilization sequence would not be useful in screening for agents that promote mRNA destabilization.

Moreover, the signal for a construct with a mRNA destabilization sequence was 3- to 5-fold less than a construct without the mRNA destabilization sequence (see Figure 4 in Kastelic et al.). Thus, prior to Applicant's disclosure, one of skill in the art would not consider combining RNA and protein destabilization sequences with a reporter gene, as the reduction in available reporter protein mRNA transcripts that can be translated in conjunction with a reduction in reporter protein half-life may not yield sufficient reporter protein for any particular assay.

In this regard, please consider that the rapid and/or significantly larger increase in induction of expression in luciferase-CL-PEST-RNA destabilization sequence constructs was unexpected (Figures 10B, 15 and 16 in Applicant's specification).

Accordingly, withdrawal of the § 103 rejection is respectfully requested.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney (612) 373-6959 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being filed using the USPTO's electronic filing system EFS-Web, and is addressed to: Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 7th day of April 2008.

Dawn M. Poole _____ Dawn M. Poole

Name Signature